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Interictal Epileptic Activity Rate in Relation with Seizure Occurrence and Sleep Stages: A Stereo-EEG Study

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Abstract

This paper presents a distributed and parallel approach for interictal spike analysis. Firstly, it allows a distributed real-time application designer to specify the desired temporal behaviour of a system, Secondly, it presents a local and global representation of interictal spike distribution for various states of patients. Thirdly it measures the relationship between interictal spikes (IS) and ictal discharges in human drug-resistant partial epilepsy. These results indicate that an analysis of sleep induced changes in depth spike activity can be useful in improving predictions concerning epileptogenicity.

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Keywords: Epilepsy; Sleep Stage; Stereo-electroencephalography (SEEG); Interictal Spike; Signal Processing; Multi-Agent System

1. Introduction

Electroencephalography (EEG) remains crucial in the identification of epileptogenic regions in refractory partial epilepsy. Interictal epileptiform spike activity is usually observed in patients with medically resistant epilepsy. Stereo-electroencephalography (SEEG) is the main investigation method for pre-surgical evaluation of patients suffering from drug-resistant partial epilepsy. SEEG signals reflect two types of paroxysmal activity: ictal activity and interictal activity or interictal spikes (IS). The relationship between interictal spikes (IS) and ictal discharges in human drug-resistant partial epilepsy is essential and a recurrent question in epiletology. This standard method (EEG recorded by depth electrodes) makes it possible to collect directly intracerebral signals of an excellent temporal resolution, which inform about the electric activity of the strategically selected structures (figure 1).

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Interictal spikes (IS) are observed at 1 per cent of non-epileptic subjects and around 60 to 90 per cent of epileptic subjects [1-3]. They are a complementary source of information in the diagnosis and localization of epilepsy. They are characterized by a brief initial phase, a sharp and strong amplitude and they occur as transitional events less than one second. The interictal spikes occurrence is higher than the seizures frequency. They appear in waves but sometimes they appear isolated. IS are classified in spikes or waves according to their duration, between 20 and 70ms, 70 and 200ms respectively. Their amplitude, significantly higher than those background activities, features them. IS clinical characterizations are based on their density, morphology, and topography. The study of the relationship between interictal and ictal activities brings a significant complement in the pre-surgical evaluation of patients suffering from drug-resistant partial epilepsy.

The present paper introduces a new method for analyzing and classifying IS over wakefulness and sleep stages. The methodology is based on a distributed, parallel and collaborative approach for an IS distribution analysis. To present preliminary results, the data used in this study were recorded from four (4) patients suffering from temporal lobe epilepsy (TLE). Temporal and spatial relationships between IS and seizure onset zones are compared during wakefulness (W), light sleep (LS) and deep sleep (DS).

2. Materials and methods

The methodology consists in transposing EEG signals vector processing in a distributed and collaborative vector platform. Each channel (SEEG signal) is associated with an agent (autonomous process) and all entities system cooperate to analyze the whole system. Our approach is based on cooperative and self-organized mechanisms at the local level (mono-IS) and global phenomenon analyses (multi-IS) as explained in the method description section.

2.1. SEEG signal recording

Stereo-electroencephalography (SEEG) signals are shown in figure 1. This investigation method used in epilepsy, makes it possible to better understand the mechanisms involved of the initiation of the paroxystic discharges in a given subset of cerebral structures and their propagation to other structures. SEEG recorded signals show sharp ictal activity and interictal activity variations, illustrating the various cerebral activities. The method uses a high temporal resolution to provide the accurate localization of distinct interictal activities in each explored structure. SEEG signals inform about various peculiarities of a structural entity, an organ or a system. Their interpretation is multifactor and therefore, is not easy; the normality for a given modality varies from a subject to another according to age, and the protocols of examinations (rest, physical stress, stimulations, etc).

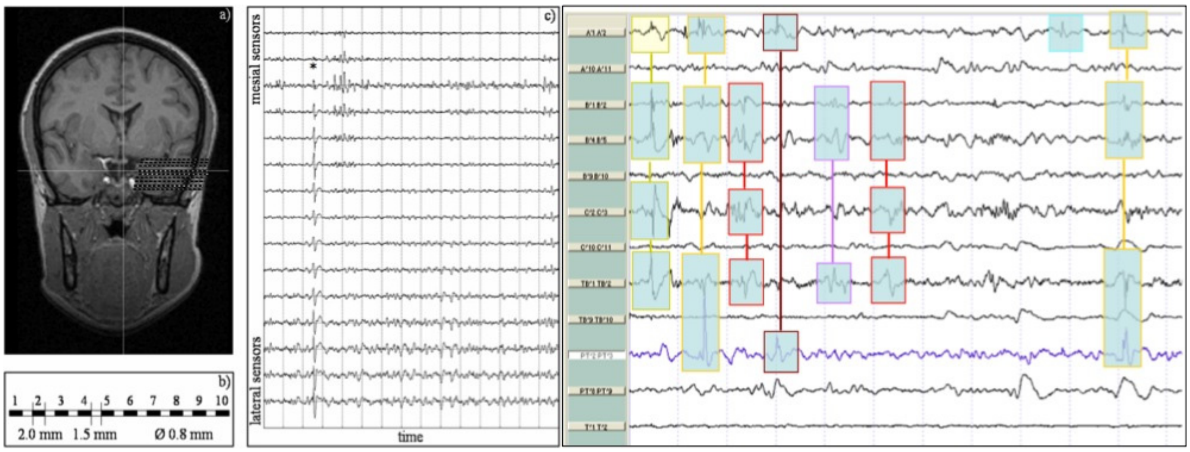

Fig. 1. (a) Intracerebral EEG, MRI showing the implementation of electrodes; (b) Plan of an electrode with staged contacts; (c) Example of recording. Multichannel event formation (multi-IS or SCAS) in the figure on the right, classification and counting in distributive collaborative approach.

2.2. Related works

Many methods have been developed to establish functional connections between brain areas in the frequency domain by using EEG or MEG recordings [4,5]. Additionally numerous methods have been designed to detect a reliable spike. Some approaches measure the sharpness of the EEG signal [6,7], while others use nonlinear modelling methods [8] or wavelets and time frequency approaches [9] to characterize the occurrence of IS. Valenti, De Lucia and Coutin-Churchman [10,11,12] propose a data mining classification technique to build an automatic detection of IS. Their method however does not take into account the precise signal form (morphology). In the spatiotemporal analysis field, Badier and Chauvel [13] propose a spatiotemporal mapping technique to study IS during the pre-surgical evaluation of their epileptogenic zone prior to surgery. Asano's work [14] shows that overall spike frequency may be increased during sleep, but the spatial distribution of spike frequency seems similar during wakefulness and sleep in children with focal seizures. White [15] proposes automated computer detection of EEG spikes and seizures to test the hypothesis that EEG spikes precede and are correlated with subsequent spontaneous recurrent seizures. To conclude, we have a variability of results and a heterogeneity of signals and methods (scalp/intracerebral EEG, automatic/manual detection) for interictal spikes analysis.

2.3. Method description

Each depth-EEG channel is considered as an agent (process) with a dynamic state, which depends on its cerebral structure activities. The cerebral structure network is considered as a system that can generate, on a temporal sliding window, interictal spikes (IS) in the form of various combinations. Let N be the number of selected EEG channels. EEG signals recording is consided as a vector signal $S(t) = [S_1(t) \ldots S_N(t)]$ observed in an interval $[0, T]$. The method consists of : *(i) characterizing IS on each EEG channel $S_i(t)$*, *(ii) determining the temporal relations between the various channels*, *(iii) studying the organization of subsets of co-actived structures (SCAS),* and *(iv) finally analyzing spatiotemporal distribution of IS. The SCAS are further analyzed statistically and a global representation of SCAS dynamics is perform as described below*.
It should be noted that $i = 1,....,N$ is the channel index, T is the observation duration, n_i is the number of spike detected on channel i, $j = 1,....,n_i$ is the index of detected events and t_{ij} is detection the time of spike j on channel i. In this approach, each signal $S_i(t)$ (figure 1) is associated to an agent that makes it sure that channel i treatment is locally implemented. Each agent has a local memory, and is able to communicate with the others by sending and receiving messages. The messages can be sent in multicast or point-to-point communication depending on the sender's choice. All processes run in parallel and in a concerted way. Process Manager is used to coordinate the processing.

The method proceeds in four steps: *(i) automatic detection of mono channel interictal spikes (mono-IS)*, *(ii) collaborative formation of subsets of co-activated structures (multichannel interictal spikes multi-IS)*, *(iii) automatic extraction of statistical co-activated structures* and *(iv) global representation of spatiotemporal distribution of IS*.

2.4. Detection of monochannel interictal spikes (mono-IS)

IS detection methods are divided into four groups : (i) *The matching pattern methods that require extensive prior knowledge of the morphology of IS and are very sensitive to changes in IS* [16]. (ii) The *methods based on parametric linear and non-linear models (auto-regressive AR)* [17]. *In the case of AR models, the background activity is the output of a filter with estimated parameters (order, poles ...).They detect the arrival of an IS when a change is observed within the space of these parameters. (iii) The heuristic methods (or mimetic methods)* [18-21] *are the most used. They go through a characterization of pieces of EEG signals by means of relevant attributes (duration, amplitude, slope, second derivative, FFT, DWT ...) before deciding if the piece in question contains a spike. (iv) The methods based on factor analysis* [22-25]*, which may be put in parallel with separation method sources.*

Analyzing the time-frequency structure of spikes shows that the sharp part of the event is characterized by a frequency spectrum extending roughly from 10 to 30 Hz (and sometimes 40 Hz). The automatic detection of mono-

IS is made as follows: The first stage consists in filtering the EEG signal by a RIF bandpass to retain sharp phases and discard the rest (background activity and slow waves). This filter also eliminates signal artifacts (mainly due to the movement of electrodes). Then the energy is calculated in the filtered signal portion with a sliding window of h samples corresponding to 100ms (h = 25 if sampling frequency equals 256 Hz). In the last stage, a Page-Hinkley algorithm [1] is used to automatically estimate the time corresponding to abrupt signal changes. Figure 1 shows the IS detection for each channel. The Page-Hinkley algorithm detects the instants of occurrence of abrupt jumps in the average value of a stationary Gaussian signal variance.

2.5. Formation of Subsets of Co-Activated Structures (SCAS or multi-IS)

Two agents are considered to be in interaction if they detect IS at the same time. The collaborative approach is proposed to extract SCAS. The analysis is made by cycles that is explored in a parallel and synchronous way on a sliding window w, which has a size of Δt. A cycle comprises three successive steps: *(i) identification of the reference time of cycle t_R, which corresponds to the estimated time of the first spike detected after the previous cycle, (ii) sliding the window at this time (t_R), (iii) extraction of SCAS by grouping all the channels, which detected a spike in this window (w). SCAS can be constituted by one or several structures (figure 1 right)*.

To group together cerebral structures, which detect a spike at the same time, each agent informs (by sending message) the other agents of its detection on the current sliding window (w). The size of the window determines the time delay below which two detections of two different agents are considered as co-activated.

3. Results

The system was implemented in ”Madkit” (Multi-agent development kit), a distributed and generic platform. To present the preliminary results, the data used in this study were recorded from 4 patients (BRE, MAL, PAS, LAU) suffering from temporal lobe epilepsy (TLE). Temporal and spatial relationships between IS and the seizure onset zone are compared during wakefulness (W), light sleep (LS) and deep sleep (DS). Figure 2 presents the mean spike rate per hour during the different stages. As depicted in figure 2, the spike rate increases with sleep depth. The overall spike rate increases from wakefulness towards sleep (W → LS → DS) for all patients.

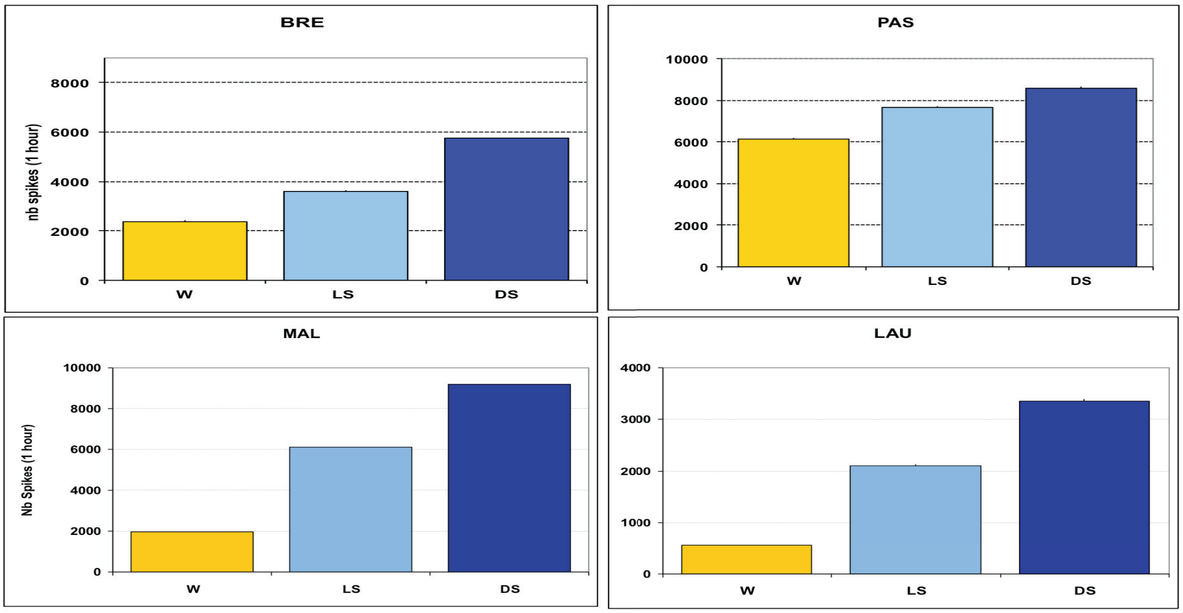

Fig. 2. Mean spike rate (/1 hour) during wakefulness (W), light sleep (LS) and deep sleep stages (DS)

Three of the four patients (BRE, MAL, PAS) underwent their seizures during wakefulness periods and one patient (LAU) underwent his seizures during sleep periods. Figure 3 represents the percentage of seizures occurring for the four patients during wakefulness and sleep stages. Figure 3 shows also the maximum number of cerebral structures involved during the three stages (W, LS and DS) and the results on simulated data for the first patient (BRE). The simulation consists in generating the same number of spikes in each channel by a random distribution model. These results show that space and temporal distributions for real data are not random but correlated; the distribution follows a well-determined law.

The platform offers access to every mono-IS event and/or multi-IS event identified during the analysis. This representation also offers access to statistical information of each event: the number of times it appears alone, the number of times it appears included in another graph (other event). The statistical information concerns the probability of occurrence of each event, the number of events and the number of different events. The different results of the statistical analyses were presented in our previous research work [25].

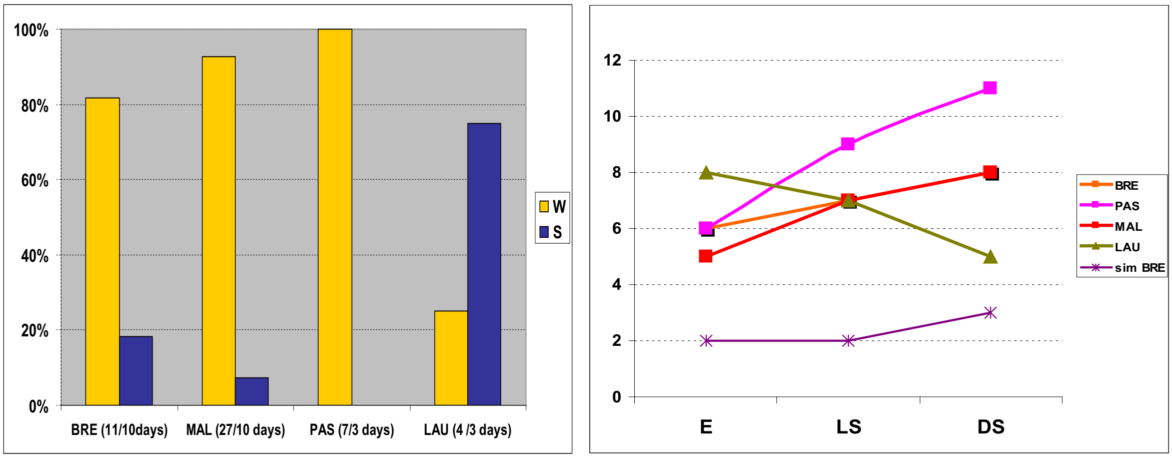

Fig. 3. (left) Percentage of seizures occurring for patients during wakefulness (W) vs. sleep(S). Three patients are seizured mainly during W, one patient has his seizures mainly during S. (rigth) Maximum number of cerebral structures involved during wakefulness (W), light sleep (LS) and deep sleep (DS) stages.

The spike distribution analysis shows that the area extent involved in the generation of interictal epileptic activity increases with sleep for patients who undergo their seizures during the wakefulness period (BRE, PAS, MAL). This trend is reversed for the patient who made his seizures during sleep periods (LAU). Does the interictal spike area extent prevent epileptic seizures ?

Is it possible that the increase of the irritative area (the spike generation area) can prevent seizures from occurring during sleeping periods?

The results clearly show an increase of the irritative area extent during sleeping periods with the patients undergoing the seizures during wakefulness (BRE, PAS, MAL). Does this phenomenon prevent seizures during sleep ? The results also show a fall in the irritative area extent with sleep for the patients undergoing their seizures during sleep. Is this second phenomenon favourable to the seizure occurrences during sleep (LAU) ?

4. Conclusion

A method to analyze and classify interictal spikes (IS) during wakefulness (W), light sleep (LS) and deep sleep (DS) has been presented. The results show that IS distribution is not random and sleep may alter the overall frequency of interictal spike. The main result presented in this paper is a contribution to the relationship between IS

and ictal discharges in human drug-resistant partial epilepsy. The area extent involved in the generation of IS increases with sleep for patients who undergo their seizures during the wakefulness period and decreases with wakefulness for the patients who undergo his seizures during sleep periods. Does the interictal spike extent area prevent epileptic seizures ? These results indicate that an analysis of sleep causes changes in depth spike activity. This can be helpful in improving predictions concerning epileptogenicity. This work prospects concern a more significant exploitation of the potentialities of the cooperative agents approach by integrating a larger cohort of patients (lateral temporal epilepsy, extra-temporal epilepsy....). It would also be interesting to analyze the morphological spikes.

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